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10/519,559	02/21/2006	Shunichi Kuroda	GRT/1035-560	7631

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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,559	KURODA ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22* is/are pending in the application.

4a) Of the above claim(s) *22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/28/04* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/31/05;9/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's election, filed on April 21, 2008. Applicant's election of Group I (Claims 12-21) and the species of a combination of eight cysteines at positions 76, 90, 137, 138, 139, 147, 149 and 221, in the reply filed on April 21, 2008, is acknowledged. Claims 10-11 have been cancelled.

2. Applicant requests withdrawal of the Examiner's finding of lack of unity because the cited Mangold *et al.* (Virology 211,535-543, 1995) does not teach any hollow nanoparticles as required by the pending claims. Therefore, the reference cited does not show that the claims lack a special technical feature.

3. Applicant's argument is not convincing. Mangold teaches HBsAg forms spherical 20-nm particles, see e.g. Para 1, right col. p. 535, and right col. p. 540. Please note that 20-nm HBsAg particles are hollow nanoparticles. Thus, the cited reference teaches the subject matter of the claims, and shows that the claims lack a special technical feature. The requirement is still deemed proper and is therefore made FINAL.

4. Accordingly, Claims 12-22 are pending. Claim 22 is withdrawn as non-elected. Claims 12-21 are considered in this Office action. Claims 12-21 read on the elected species of replacement of eight cysteines at positions 76, 90, 137, 138, 139, 147, 149 and 221.

Specification

Sequence Rules

5. The instant application is not fully in compliance with the sequence rules, 37 C.F.R. §§

1.821-1.825, because each disclosure of a sequence embraced by the definitions set forth in the rules is not accompanied by the required reference to the relevant sequence identifier (i.e., SEQ ID NO:), see Table 1, Figures 1 and 2, for example. Figures 1 and 2 show amino acid sequences, but there are no references to sequence identifiers.

Information Disclosure Statement

6. The information disclosure statements submitted on January 31, 2005, and September 20, 2005, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. The initialed and dated copies of Applicant's IDS form 1449 are attached to the instant Office action.

Foreign Priority

7. Applicant's provision of foreign priority documents Japan 2002-191386 and Japan 2003-183863 is acknowledged. It is noted, however, that English translation has not been provided. Therefore, it is not clear whether the foreign priority documents provide written description for the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112, first paragraph. Therefore, the priority date is deemed to be the filing date of the priority application PCT/JP03/08244 (06/27/2003).

Claim Rejections - 35 USC § 112, first paragraph-Scope of enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making HBsAg nanoparticle, does not reasonably provide enablement for a drug comprising a nanoparticle and a unknown substance for treating any diseases and does not reasonably provide enablement for making nanoparticles comprising unknown particle-forming protein containing modified cysteine residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught

one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

10. Claims 20 and 21 are directed to a drug comprising any nanoparticles formed of any particle-forming protein and a substance, wherein in the protein contains at least one modified cysteine residue, and wherein in the substance comprising a gene. To support the claims, the specification disclosed a nanoparticle comprising HBV HBsAg and a GFP gene. However, the specification has not provided any teaching or working examples indicating that HBsAg/GFP can be used for treat any specific diseases.

11. The art does not support a notion that any nanoparticles comprising any unknown particle-forming protein and a substance is a drug. Rather, the prior art teaches pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for its physiological activity. The state of the art indicates "The process of drug discovery and development is a long, complex and multi-stage process where odds of success, in retrospect, are low. For drug, in general, only 20% of drug discovery projects leads to a clinical candidate and only 10% of compounds that enter clinical development achieve registration" (Pauwels, 2006). More importantly, Pauwels points out: "Analysis of the reasons for apparently low and even declining success rate reveals that projects mainly fail because drug candidates prove inactive in animal models or in patients, display unacceptable toxicity or cause undesirable side-effects upon *in vivo* administration" (Pauwels, 2006). Thus, the state of the art has shown that drug development is unpredictable; neither is the alleged drug comprising any nanoparticles that contain any substances.

12. The state of prior art also teaches that it is unpredictable if a particle-forming protein can encapsulate a foreign substance while maintaining its structure of a nanoparticle. The structure of foreign substances can affect particle formation. For example, Ward *et al* (Virus Genes, Vol. 23: p. 97-104, 2001) tried to package the hepatitis C virus (HCV) core protein into HBsAg particles. Ward *et al* found that only limited chimeric proteins were packaged into viral particles, due to poor expression and the size limit to the insert (see in particular the abstract and Fig. 3). Therefore, it is unpredictable in the art whether or not an uncharacterized nanoparticle can encapsulate any particular uncharacterized substances. The specification has provided little guidance as to what are the structural requirements for "a substance" to be fused to or packaged into any particle-forming proteins.

14. Since the scope of Claims 20 and 21 clearly cover the alleged drugs comprising undefined nanoparticles for treating un-specified diseases in human, in order for the full breadth of the invention to be enabled, a skilled artisan would have to make and test all particle-forming proteins to see if they can encapsulate any substance, and test them to see if they can be "a drug" for treating undefined diseases. Such drug screening would entail an undue amount of experimentation. In view of the empirical and unpredictable nature of drug development and lack of guidance and working examples in the specification, one skilled in the art would not know how to make and use the alleged drugs of the instant invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 12-14 and 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Mangold et al. (Virology 221, 535-543, 1995).

17. Mangold teaches a nanoparticle formed of a hepatitis B virus surface antigen (HBsAg), which comprises at least one cysteine residue at each of positions **76, 90**, 107, 121, 137, 138, 139, 147 and 149, and **221** is replaced by Ala (a hydrophobic amino acid), wherein Cys90 is located in the ER membrane, Cys 107, 121, 137, 138, 139, 149 and 221 are located in ER-lumen (inside the particle), and Cys 76 is located in cytoplasm (outside the particle), See. e. g. Abstract, and Para 1, right col. p. 540). These teachings anticipate Claims 12-14.

18. Mangold teaches that the HBsAg particles are made by expressing HBsAg gene with a replacement of native cys codon by an ala codon in COS-7 cell (a eukaryotic cell) (Para 2, left col. p. 536). This teaching anticipates Claims 17-19.

19. Claims 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Primi (US 6,172,193, Date of Patent: Jan 9, 2001).

20. Primi teaches an isolated mutant HBsAg protein or particle, wherein at least one of the cysteines at positions 121, 147 and 149 is replaced by tyrosine (See e. g. Col. 4 and Table 1). Therefore, Claims 12-14 are anticipated by Primi.

20. Claims 12, 17, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by

Hatton (J. Virology, 66(9):5232-5241, 1992).

21. Hatton teaches mutated HBV core antigen particles (core particle, HBc), Δ-172, Δ-162, Δ-157, and Δ-149, in which cys183 is deleted, See e. g. Para 2, left col. p. 5233, and Fig. 1A. HBc particles (p21.5) are made by gene expression in *E.coli*., or in *Xenopus* oocytes (animal cell), See e.g. p. 5233. The mutated HBc particle can package (encapsulate) viral RNA into the core particles (See *Results*, *A single Arg block mediates RNA binding and encapsulation*, pp 5234-5235. Thus, Hatton shows that these mutated HBc particles are substance (gene)-containing particles.

22. The specification [0013] recites: It is preferable that the Cys residues be modified by substitution by other amino acids. Alternatively, the Cys residues may be modified by deletion.

23. In view these teachings, Claims 12, 17, 20 and 21 are anticipated by Hatton.

Claim Rejections – 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mangold (Virology 221, 535-543, 1995), as applied to Claims 12 and 14, and in view of Mangold (J. Virology, 67(8):4588-4597).

27. Claim 15 requires that the nanoparticle of Claim 14 contains at least one cys present inside or outside the particle is replaced with Ser. Claim 16 reads on the elected species of replacement of eight cysteines in HBsAg at positions 76, 90, 137, 138, 139, 147, 149 and 221.

28. The relevance of Mangold (1995) is set forth *supra*. In addition, Mangold teaches that replacement of **Cys 76, 90 and 221** of HBsAg are dispensable for HBsAg particle assembly and secretion, see Para 1, col. right, p. 540. In addition, Cys 138 reduced the efficiency of secretion to a very low level, replacement of Cys 137, 138, 148 and 149 with Ala has either little (barely detectable) or no effect on the particle secretion efficiency. Importantly, Mangold teaches that HBsAg mutants **Cys147/149Ala**, **Cys 149**Ala and **Cys137/138/139Ala** significantly reduce their antigenic reactivity to HBsAg-specific antibodies, See e.g. p. 539 and Table 2.

29. Mangold explicitly suggests that HBsAg containing cysteine mutations can be used for therapeutic and diagnostic aims. Mangold teaches that HBsAg containing cysteine mutations are non-responsive to HBsAg antibody, so that they can escape the antibody against them in a patient, when they are used as a vaccine or treatment agent (See right col. p. 542).

30. Mangold (1993) teaches that cysteins present inside, such as cys48, cys 65 and cys69, or outside, such cys121, cys 124, cys149, the particle can also replaced with Ser (See e.g. right col. p. 4595, and Fig.3).

31. Mangold does not explicitly teach replacing all eight cysteines in HBsAg at positions 76, 90, 137, 138, 139, 147, 149 and 221 together.

32. It would have been obvious to one of ordinary skill in the art to modify HBsAg particle as an intended therapeutic agent (or a carrier) by replacing native cysteines with Ala at positions 76, 90, 137, 138, 139, 147, 149 and 221 in order to bypass the pre-existing antibody to native HBsAg as taught and suggested by Mangold. One would have been motivated to do so and have a reasonable expectation of success, given the knowledge that cysteines in theses positions are dispensable for particle formation, secretion, and also given that replacement of cysteines at these positions can reduce the immunogenicity of native HBsAg, as taught by Mangold. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Remarks

33. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The

examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner
July 7, 2008